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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,954	02/15/2002	Akira Kaji	K0448/7012	3440

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,954	KAJI ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,28 and 47-49* is/are pending in the application.

4a) Of the above claim(s) *9-11,18,23,24,28 and 47-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-17 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-24, 28, and 47-49 are pending in the application.

Election/Restriction

[2] Applicants' election without traverse of the invention of Group IV, claims 1-8, 12-17, and 19-22, filed August 02, 2004, is acknowledged.

[3] Claims 9-11, 18, 23-24, 28, and 47-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[4] Claims 1-8, 12-17, and 19-22 are being examined on the merits.

Information Disclosure Statement

[5] With the exception of references C7 and C33, references cited in the information disclosure statement (IDS) filed March 12, 2002 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action. Reference C7 cannot be located in the application and reference C33 is a duplicate of reference C3.

Priority

[6] Applicants' claim to foreign priority under 35 USC 119(a)-(d) to Japanese application 11-158637, filed June 04, 1999, is acknowledged. It is noted that June 04, 2000 falls on a Sunday, while June 05, 2000 falls on a Monday, thus the chain of priority

is considered valid. A certified copy of the foreign priority document has been filed in the instant application.

Specification/Informalities

[7] The specification is objected to in the disclosure of "the structure coordinate of RRF of the present invention as provided in Table 7" (*e.g.,* page 23, bottom) as Table 7 lists the results of a screen for inhibitory compounds.

Claim Objections

[8] Claims 1-8, 12-14, 16-17, and 19-22 are objected to in the recitation of "RRF". Abbreviations, unless otherwise obvious should not be recited in the claims without at least once reciting the entire phrase, *i.e.,* "ribosomal recycling factor" for which the abbreviation is used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[9] Claim(s) 1-8, 12-17, and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 1 (claims 2-8, 12-17, and 19-22 dependent therefrom) is indefinite as the claim attempts to recite a process without setting forth any steps involved in the process. It is suggested that applicants clearly set forth the method steps that are required to practice the method. See Case 6 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" (pp. 69-73) at www.uspto.gov/web/tws/wm4/wm4_index.htm.

[b] Claim 1 (claims 2-8, 12-17, and 19-22 dependent therefrom) is indefinite in the recitation of "active site, an accessory binding site or a pocket of an RRF protein" as it is unclear from the claims and the specification as to those residues of an RRF protein that are considered to be active site residues, accessory binding site residues, or RRF binding pocket residues. While it is noted that the specification defines "active site" as any optional site or all sites in RRF... ...to which ribosome and its complex binds and at which decomposition of the substrate occurs" and that the active site is "in the vicinity of at least amino acid residue 110, 129, and 132 by use of SEQ. ID. No. 1" (p. 19) and defines "pocket" as "a hollow that is present on an RRF protein surface and also includes in addition to a binding pocket that is present on a binding site or accessory binding site of an RRF protein, other pockets that do not participate in binding to a substrate and so forth upon the expression of the activity of RRF" (pp. 19-20). However, even in view of these definitions it is unclear as to the meaning of the terms. It is suggested that applicants clarify the meaning of the terms.

[c] Claim 1 (claims 2-8, 12-17, and 19-22 dependent therefrom) is indefinite in the recitation of "computationally evaluating" as it is unclear as to how the computational evaluation is carried out, *e.g.,* is the computational evaluation performed mentally or with the aid of a computer? It is suggested that applicants clarify the meaning of the term.

[d] Claim 1 (claims 2-8, 12-17, and 19-22 dependent therefrom) is indefinite in the recitation of "a chemical entity of RRF protein" as it is unclear as to whether the "chemical entity" is a potential RRF-binding compound as suggested by the specification or is an "entity" of an RRF protein itself as suggested by the claim. It is suggested that applicants clarify the meaning of the term.

[e] Claims 1-8, 12-13, 14 (claim 15 dependent therefrom), 16-17, and 19-22 are indefinite in the recitation of "RRF protein." The specification defines "RRF protein" as being "an RRF protein having an enzyme activity in an ordinary state" (p. 13). However, it is unclear from this definition as to the proteins that are intended to be encompassed by the term "RRF protein." It is suggested that applicants clarify the meaning of the term.

[f] Claims 2 and 14 (claim 15 dependent therefrom) are unclear in the recitation of "the RRF protein itself" as it is unclear as to the RRF that this term references. It is suggested that applicants clarify the meaning of the term.

[g] Claims 7 and 22 are confusing in reference to Table 7 as describing a structure coordinate. Table 7 (p. 57 of the specification) appears to list results of *in vitro* RRF inhibition studies.

[h] Claims 8 and 12 are indefinite in the recitation of "derived from" as it is unclear as to the meaning of the term. For example, is the term meant to be interpreted as "isolated from?" The term is also confusing in the context of the claim, *i.e.,* how does one derive a protein crystal from a bacterium?

[i] Claim 15 is confusing as it is unclear as to how the heavy atom derivative is formed by "reaction of a compound" as recited in the claim. It is unclear as to how the compound reacts and whether the reaction is with itself or with a protein. It is suggested that applicants clarify the meaning of the claim.

[j] Claim 19 is unclear in the recitation of "compound characterized by the chemical entity bound to the active site." It is suggested that applicants clarify the meaning of the term.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[10] Claims 1-8, 12-17, and 19-22 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. The claims are drawn to a method for designing a compound capable of binding to an RRF protein by computational evaluation.

The specification discloses that protein biosynthesis is a function that is indispensable for biological activities of all cells (p. 1, bottom) and that RRF is catalyzes

ribosome recycling, which is the fourth step of protein biosynthesis (pp. 1-2). Applicants indicate it is possible that in eukaryotes the dissociation of a protein translation termination complex is catalyzed by a factor other than RRF and that "there is an expectation [of RRF] as a target of especially a new type of antibiotic" (p. 2).

While there may be an "expectation" that RRF may be a target for a new type of antibiotic, the specification provides no correlation between compounds that could be identified by the claimed methods and an ability to act as antibiotics or evidence that RRF *is* a target for antibacterial activity. Even assuming *arguendo* RRF is a target for antibacterials, there is no indication that the RRF used in the generation of structural coordinates (Table 8) is from a pathogenic bacterium such that inhibitors of the RRF having the structural coordinates of Table 8 would be useful in the production of antibacterial agents.

Thus, one of skill in the art would recognize that further experimentation is required to identify a "real world" use for the claimed methods. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Thus, the claimed invention is not supported by a specific and substantial asserted utility and the examiner knows of no well-established use for the claimed invention.

[11] Claims 1-8, 12-17, and 19-22 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[12] Claims 1-8, 12-17, and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to a method for designing a compound capable of binding to a genus of RRF proteins by computational evaluation of a chemical entity on the basis of a genus of structure coordinates obtained from an RRF protein crystal. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or

chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification discloses only a single representative species of the genus of recited structural coordinates obtained from an RRF protein crystal, *i.e.,* the structural coordinates of Table 8, which were obtained from a crystal of *T. maritime* RRF of SEQ ID NO:1 having space group $P4_32_12$, the unit cell dimensions of a=b=47.3Å and c=297.6Å, and a crystal size of 0.3 x 0.3 x 0.5 mm. The specification fails to describe any additional representative species of the recited genus of structural coordinates obtained from an RRF protein crystal. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the recited genus of structural coordinates obtained from an RRF protein crystal encompasses species that are widely variant, including structural coordinates obtained from any RRF protein crystal, including RRF proteins that have yet to be isolated and mutants and variants of any RRF protein having any space group and unit cell dimensions. As such, the disclosure of the single representative species of structural

coordinates obtained from an RRF protein crystal is insufficient to be representative of the attributes and features of *all* species encompassed by the recited genus of structural coordinates obtained from an RRF protein crystal. Given the lack of description of a representative number of structural coordinates obtained from an RRF protein crystal, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[13] Even if the claimed methods are shown to have a specific and substantial utility, the following rejection applies. Claims 1-8, 12-17, and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP §

2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass methods for design of an RRF-binding compound capable of binding to any active site, any accessory binding site, or any pocket of an RRF protein using any structure coordinate obtained from any RRF protein crystal from any source, including mutants and variants, having any space group and unit cell dimension.

- The lack of guidance and working examples: Regarding the active site, accessory binding site, or pocket of an RRF protein, it is noted that the specification fails to teach those amino acids that are considered to comprise the active site, accessory binding site, or pocket of an RRF protein. Such guidance is necessary in making a determination of the amino acid side chains or functional groups that interact with a potential binding compound. While the specification provides *in vitro* analysis of various RRF mutants (pp. 45-51) in an example entitled "Presumption of the active site of RRF" and implies that an active site residue is one of Arg110, Arg129, or Arg132 (p. 11), it remains unclear from the results presented therein as to the amino acids that are considered to comprise the RRF active site binding pocket. Regarding the structural coordinates, the specification discloses only a single working example of the recited structural coordinates, *i.e.,* the structural coordinates of Table 8, which were obtained from a crystal of *T. maritime* RRF of SEQ ID NO:1 having space group $P4_32_12$, the unit cell dimensions of a=b=47.3Å and c=297.6Å, and a crystal size of 0.3 x 0.3 x 0.5 mm. Other than this single working example, the specification fails to provide additional

working examples of structural coordinates obtained from RRF protein crystals. Also, it is noted that the specification fails to provide even a single working example of the claimed method.

- The high level of unpredictability in the art: The prior art acknowledges the unpredictability in obtaining diffraction quality crystals. For example, at the time of the invention, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that protein crystallization is usually quite difficult to achieve and details reasons supporting their assertion. Thus, although the specification teaches methods for crystallization of two RRF proteins, one of skill would recognize the unpredictability in obtaining the structural coordinates from any RRF protein from any source, including mutants and variants thereof. Without knowledge of a protein's binding pocket, it must first be identified prior to design of binding compounds. In this case, not only an active site, but also any accessory binding sites and any RRF pockets must also be identified. While computer programs for predicting a protein's binding pocket exist, there is no reliable measure of the accuracy of such programs in selecting the correct binding pocket. Such programs are likely to select multiple binding pockets, thus there is a high level of unpredictability in designing an appropriate compound as encompassed by the claims. Further, it should be noted that it is highly unpredictable based on purely *in silico* data as to whether an inhibitor will be a competitive, uncompetitive, or a non-competitive inhibitor.

- The amount of experimentation required: It is not routine in the art to design a binding compound without knowledge of its binding pocket. Further, it is not routine to

crystallize all proteins from any source including all mutants and variants thereof to obtain structural coordinates for design of binding compounds.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the significant amount of experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. As such, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It should be noted that, if it is found that the specification enables the claimed invention, a rejection under 35 U.S.C. may be necessitated according to Case 6 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" (pp. 69-73) at www.uspto.gov/web/tws/wm4/wm4_index.htm.

Comments

[14] In this case, the 3-D coordinates of *T. maritima* RRF were known in the art at the time of the invention (see Selmer et al. *Science* 286:2349-2352; cited as reference C3 on the IDS filed March 12, 2003), computer programs that predict protein binding pockets were known at the time of the invention, and *in silico* screening programs using a predicted protein binding pocket were known in the art at the time of the invention. However, it is the examiner's position that the specification and the prior art do not enable the claimed method at least because the prediction of the RRF binding pocket using the structural coordinates as disclosed at Table 8 would require undue experimentation. As the specification and the prior have failed to enable the claimed invention, a rejection of the claims under 35 U.S.C. 103 in accordance with part A4 of Case 6 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" (pp. 72-73) has not been raised because a claimed method cannot be obvious if it is not enabled. It is noted that if it is found that the specification enables the claimed invention, a rejection under 35 U.S.C. may be necessitated according to Case 6 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" (pp. 69-73) at www.uspto.gov/web/tws/wm4/wm4_index.htm.

[15] If applicants dispute the examiner's assertion that the 3-D coordinates of *T. maritima* RRF were known in the art at the time of the invention (Selma et al., *supra)* based on the earlier filing date of a foreign application, applicants should provide an

English-language translation of the Japanese priority document in order to perfect priority under 35 U.S.C. 119(a)-(d).

Conclusion

[16] Status of the claims:

- Claims 1-24, 28, and 47-49 are pending.
- Claims 9-11, 18, 23-24, 28, and 47-49 are withdrawn from consideration.
- Claims 1-8, 12-17, and 19-22 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Primary Examiner
Art Unit 1652
09-13-04